

Development of Selective Opioid Receptor Antagonists

F. Ivy Carroll

Studies have shown that JD_{Tic} is a selective, orally active kappa opioid receptor antagonist. Based on animal pharmacology studies, JD_{Tic} has potential therapeutic utility for preventing relapse to cocaine and treating depression. Other animal studies suggest that JD_{Tic} may also have potential therapeutic utility for treating alcoholism during abstinence. JD_{Tic} also appears to have anxiolytic effects: it dose-dependently increased open-arm exploration without affecting open-field (OF) paradigms, and it decreased condition fear in the fear-potentiated startle (FPS) test. Recent structure activity studies have led to several JD_{Tic} analogs that possess $K_{e,s}$ of less than 1.0 nM at the kappa opioid receptor in the [³⁵S]GTP γ S in vitro efficacy assays and greater than 100-fold selectivity for the kappa opioid receptor relative to the mu and delta opioid receptors. The more potent and selective analogs were shown to be active in the antagonism of U50,488-induced diuresis.

The presentation will review studies that led to the selection of JD_{Tic} as a pharmacotherapy for cocaine relapse and will present structure activity relationship studies directed toward the development of other selective kappa opioid receptor antagonists.